Health-related quality of life in dermatology: measurement, interpretation and application
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GENERAL INTRODUCTION
INTRODUCTION
The importance of the use of patient reported outcomes (PROs) in research, clinical practice, and health care management is increasingly being recognized. A PRO is a measurement of any aspect of a patient’s health status that is directly assessed by the patient without the interpretation of the patient’s response by anyone other than the patient. Examples of PROs include illness perceptions, satisfaction with care, and health-related quality of life (HRQoL). PROs are most commonly assessed by means of self-administered questionnaires, termed instruments or patient reported outcome measures (PROMs). One of the most commonly used PROs in health care research and clinical practice is HRQoL.

Health-related quality of life
Following the definition of the World Health Organization, HRQoL entails at least three domains and reflects patients’ evaluation of physical, mental and social functioning and well-being. Examples include physical discomfort, psychological stress, and social interaction. HRQoL is particularly relevant in patients with a chronic skin disease, such as acne, eczema, hidradenitis suppurativa, psoriasis, and vitiligo, where dermatological treatment can only offer a temporary suppression or remission of symptoms. When treatment is not expected to cure the disease and where patients’ well-being is adversely affected, dermatological treatment is increasingly directed towards both a decrease of disease severity and an increase of patients’ HRQoL.

Since HRQoL is generally considered to be an important PRO in research and clinical practice, understanding of the concept HRQoL and the measurement of HRQoL is essential. Reliable, valid, and interpretable instruments are needed to adequately measure HRQoL. In addition, knowledge of the interpretation of HRQoL data, as well as knowledge of the relevance and application of HRQoL measurement, are prerequisites for the routine use of a HRQoL intervention in clinical practice.

Measurement of health-related quality of life in dermatology
HRQoL instruments generally consist of a number of multiple-response questions or items. Response options often refer to frequency, intensity, or severity. The measurement of HRQoL with such instruments results in one or more (domain) scores reflecting patients’ HRQoL. A large number of HRQoL instruments exist. Among these instruments a distinction can be made between generic instruments and specific instruments. Generic instruments, such as the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), can be applied to different kinds of disease populations as well as the general population. Specific instruments comprise dermatology-specific and disease-specific instruments. Dermatology-specific instruments, such the Dermatology Life Quality Index (DLQI), the Skindex-29, and the Skindex-17, have been designed for various skin diseases. Disease-specific instruments have been developed for particular skin diseases, for example the Psoriasis Index of Quality of Life (PSORIQoL) for psoriasis patients and the Quality of Life Index for Atopic Dermatitis (QoLIAD) for patients with atopic dermatitis. Specific instruments capture relevant domains and aspects of HRQoL that are considered to be important to patients with skin diseases that might not be captured with generic instruments.
The DLQI, introduced in 1994, was the first dermatology-specific instrument to measure HRQoL in skin diseases. This practical tool consists of ten items. An overall sum score can be calculated, ranging from 0-30, with higher scores indicating a greater impairment of patients’ HRQoL. The DLQI is the most commonly used instrument in dermatological research, and it has played a major role in the development of HRQoL measurement in dermatology over the years.

Knowledge of measurement properties has evolved. The Skindex-29, developed in 1997 by Professor M.M. Chren and colleagues, was the first multi-dimensional, dermatology-specific HRQoL instrument. It consists of 29 items that are combined to form three domains: Symptoms (consisting of 7 items), Emotions (10 items), and Functioning (12 items). Items include statements, and inquire about the frequency of these statements during the past week. Responses are given on a five-point response scale, ranging from ‘never’ (0) to ‘all the time’ (100), with higher scores indicating lower levels of HRQoL. Several reviews suggest that the Skindex-29 is considered to be the instrument of choice in dermatology.

Before a HRQoL instrument can be adequately used in research and clinical practice, the psychometric quality (i.e., measurement properties) needs to be tested to ensure the reliability (i.e., measurement precision) and validity (i.e., measuring what is intended) of the instrument. Psychometrics is the methodology concerning the theory and technique of the design, construction, validation, administration, analysis and interpretation of an instrument that measures a certain construct such as HRQoL. Most HRQoL instruments are developed and psychometrically tested according to classical test theory models, and so are the DLQI and the Skindex-29.

To further contribute to the quality of HRQoL measurement in dermatology, basic knowledge of the concept HRQoL, its measurement instruments and the psychometric quality of these instruments is important, especially for clinicians or junior researchers who are relatively unfamiliar with this concept.

Interpretation of health-related quality of life scores

Once an instrument is found to be reliable and valid, an important next question is: what is the clinical meaningfulness of HRQoL scores and how can scores be interpreted by clinicians? Questions on the interpretation of HRQoL scores are challenging because, in the absence of a unit of measurement, a HRQoL score in itself has little or no direct meaning and the interpretation of scores is not immediately straightforward. In general, there are two types of methods to establish the clinically meaningfulness of HRQoL scores: anchor-based methods and distribution-based methods. Anchor-based methods examine the relationship between scores on a HRQoL instrument and an independent measure or anchor, whereas distribution-based methods rely on the score distributions of clinically distinct subgroups of patients.

Contrary to the classical test theory model, that is directed to sum scores to estimate patients’ HRQoL, modern test theory models, such as item response theory (IRT) models and Rasch measurement, focus on the properties of individual test items as the main source of information on patients’ HRQoL. Modern test theory models incorporate statistical tests for uni-dimensionality of an item set. In a study by Professor T.E.C. Nijsten and colleagues, for example, the Rasch measurement model was used in testing the Skindex-29. This resulted
in a reduced 17-item version. Modern test theory models can also be used to provide further insight into the clinical meaningfulness of HRQoL scores. They provide directions on how to score items, and inform whether weighting the items on their discriminative ability is needed. In addition, modern test theory models can be used to estimate ‘person ability’ and ‘item difficulty’ and can place items in the order of these estimates. The resulting hierarchy of items is an aid in understanding the differences in HRQoL scores. With these advantages over classical test theory models, modern test theory models are at present generally acknowledged as a step forward in instrument development and testing, and allow the use of the best available instruments in health care research and clinical practice. To date, however, little is known about the clinically meaningfulness of Skindex-29 scores, or differences herein.

**Health-related quality of life application in clinical practice**

The measurement of HRQoL is considered to be specifically relevant for (i) patients with a chronic skin disease, (ii) who may require a long-term treatment, (iii) where social visibility plays an important role, and (iv) when the skin disease is severe. It is known that, for example, patients with psoriasis and eczema may suffer considerably from their skin disease in terms of HRQoL. Patients with other chronic skin diseases, such as acne, hidradenitis suppurativa, and vitiligo, may also experience a considerable negative impact on their HRQoL. In patients who are expected to experience a negative impact of their skin disease on HRQoL, it is important that dermatologists do not exclusively focus on the physical symptoms but also on the effects of the skin disease on HRQoL. Aspects such as ‘depression’, ‘social interaction’ and ‘shame’ often remain unknown to clinicians. However, the application of HRQoL measurement in dermatological practice is not yet customary. At busy dermatology clinics, clinicians might experience the measurement of HRQoL as time consuming or prohibitive. They may also experience practical burdens, such as extra paper work, and the need for assistance to instruct patients in completing the questionnaires. In order to effectively apply a HRQoL intervention in clinical practice, it is essential for clinicians to recognize the relevance of HRQoL measurement, to know which patients might benefit most from it, and to know how HRQoL measurement can be best applied in clinical practice.

Among others, Professor G. Velikova and colleagues and Dr S.B. Detmar and colleagues investigated the effects of HRQoL measurement in clinical oncology practice. They reported a positive impact on patients’ well-being and doctor-patient communication, and a clinically meaningful improvement in patients’ HRQoL. Dr J.M. Valderas and colleagues conducted a systematic review on the impact of PRO measurement in different clinical settings, such as internal medicine, oncology, and primary care. They reported that no apparent conclusion could be drawn because included studies were heterogeneous in types of setting, participants, intensity of intervention, and diversity of outcomes. Despite these findings, positive aspects of the impact of PRO measurement in clinical practice were found, such as the facilitation of doctor-patient communication and the detection of physical or psychological problems, and further research was suggested. At present, evidence on the effectiveness of a HRQoL intervention in dermatological practice is missing.
AIMS AND OUTLINE OF THE THESIS

The overall aim of this thesis is to contribute to the improvement of HRQoL of patients with a chronic skin disease. The focus of the thesis is on (i) the measurement of HRQoL in dermatology, (ii) the interpretation of HRQoL data, and (iii) the application of a HRQoL intervention in clinical practice.

The aim of the first part of the thesis is to further contribute to the quality of HRQoL measurement in dermatological research and clinical practice, by providing an introduction to the concept HRQoL and the related methodology of the measurement of HRQoL (chapter 2.1). The aims of the second part are to facilitate the interpretation of HRQoL scores and of score differences using the Skindex-29 (chapters 3.1 through 3.4). The aims of the third part are to support the application of HRQoL measurement in clinical practice (chapter 4.1), and to investigate the efficacy of a HRQoL intervention in dermatological practice (chapters 4.2 and 4.3).

In 2008, the European Academy for Dermatology and Venereology (EADV) Taskforce on Quality of Life was established by Professor A.Y. Finlay and Dr T. Schaefer (http://www.eadv.org/). The objective of this Taskforce is to contribute to the scientific knowledge and measurement of PROs in dermatology. The Taskforce is encouraging the application of HRQoL instruments in research and clinical practice. The aim of the first manuscript that was written on behalf of the Taskforce is to contribute to the overall quality of HRQoL measurement in dermatology. Chapter 2.1 is a review article that provides an introduction to the concept and methodology of HRQoL. An overview of the most commonly used HRQoL instruments in dermatology is given. Background information is provided on the psychometric quality of these instruments, as well as on the selection process of a HRQoL instrument. Furthermore, it discusses the lack of consensus regarding the preferred HRQoL instrument to be used in dermatology.

As indicated, little is known about the interpretability of Skindex-29 scores. Our aim is to facilitate the interpretation of Skindex-29 scores by identifying clinically meaningful cut-off scores. An anchor-based method is used to establish these cut-off scores. In chapter 3.1 we present the results of a multicenter survey study, determining the most optimal cut-off scores for the Skindex-29 domain and overall scores indicating patients with (very) severely impaired HRQoL. Patients with scores equal to or above the established cut-off scores are significantly affected by their skin disease.

In a commentary on the interpretation of Skindex-29 scores presented in chapter 3.1, Professor M.M. Chren emphasized the relevance of establishing Skindex-29 cut-off scores for mild and moderate impairment of HRQoL in addition to those for (very) severe impairment (Addendum I). Chapter 3.2 is a response to Professor M.M. Chren and presents additional empirical data on Skindex-29 cut-off scores that are indicative for mildly and moderately impaired HRQoL, in addition to the cut-off scores for (very) severe impairment.

In another commentary by Dr F. Sampogna and Dr D.D. Abeni, the categorization of Skindex-29 scores using an anchor-based method is compared with the categorization of scores using a distribution-based method. Differences and implications between these two categorization methods are discussed (Addendum II). Unfortunately, the authors
misinterpreted our findings, leading to an incorrect categorization of cut-off scores. Chapter 3.3 is a Letter to the Editor reflecting on this commentary, and a correct overview of the categorization of Skindex-29 cut-off scores is provided.

An important limitation in HRQoL research in dermatology is the lack of evidence concerning which difference in Skindex-29 scores is clinically meaningful. In addition to this, the reduction of the Skindex-29 into the 17-item version, by using the Rasch model, may have resulted in the deletion of valuable items, as the Rasch model does not permit items to differ in their level of discrimination. These items may provide important information to be used in the clinical management of dermatology patients. Our aim is to examine the discriminating capacity of the Skindex-29 items, and to determine the clinical meaningfulness of differences in Skindex-29 scores. Chapter 3.4 presents the results of an empirical study using a specific extension of the IRT model, called the one-parameter logistic model (OPLM). OPLM is used to identify clinically meaningful differences in Skindex-29 scores.

The application of HRQoL measurement in dermatological practice is not yet customary and many practical and attitudinal barriers need to be overcome. Our aim is to support the application of HRQoL measurement among clinicians. Chapter 4.1 is a didactic article that adds to this application. It describes the relevance of HRQoL measurement to dermatological practice, it illustrates which patients would benefit most from routine HRQoL measurement, and it reflects on how HRQoL measurement can be applied in clinical practice.

Evidence on the evaluation of the effectiveness of a HRQoL intervention in dermatological practice is missing. The aim of our study is to investigate the efficacy of a HRQoL intervention in clinical practice. Chapter 4.2 presents a study protocol describing the rationale and design of a multicenter randomized controlled trial (RCT) that investigates the efficacy of a HRQoL intervention in patients with moderate to severe psoriasis undergoing biologic treatment during a treatment period of 48 weeks.

Chapter 4.3 presents the results of this multicenter RCT. Psoriasis patients who received a biologic treatment with the HRQoL intervention (that is, the completion of the electronic Skindex-29 and communication about the resulting data with their dermatologists) are compared to patients who received a biologic treatment alone. The effect of the HRQoL intervention on, primarily, patients’ HRQoL and doctor-patient communication, and secondary on health status and disease severity, is examined after 24 and 48 weeks respectively.

Chapter 5 is a summary of chapters of the thesis.

The thesis concludes with a general discussion reflecting on the main findings and limitations, and future perspectives are discussed (chapter 6).
REFERENCES


